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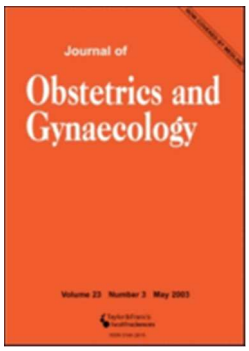

Thickened endometrium without postmenopausal bleeding – determining an optimum threshold for prediction of hyperplasia and cancer

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Thickened endometrium without postmenopausal bleeding – determining an optimum threshold for prediction of hyperplasia and cancer

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Abstract

There is lack of consensus about the significance and management of an incidental finding of endometrial thickness (ET) >4mm on transvaginal ultrasound scan in postmenopausal women without postmenopausal bleeding (PMB). The data of 1995 consecutive women attending PMB clinic were collected prospectively; of them 81 (4.1%) were referred because of ET>4mm without PMB. The prevalence of endometrial atypical hyperplasia and cancer was 4/81 (4.9%) and polyp was 20/81 (24.7%). On using Receiver Operator Characteristic curve, the diagnosis of endometrial atypical hyperplasia and cancer using ET threshold of ≥10mm had sensitivity of 100% (95% CI=40-100%), specificity of 60% (95% CI=48-71%) with AUC=0.8 (95% CI=0.66-0.93), p<0.04. For the 35 women with ET ≥10mm, the prevalence of endometrial atypical hyperplasia and cancer was 4/35 (11.4%) and benign endometrial polyps was 16/35 (45.7%). The use of ≥10mm ET threshold to prompt investigations did not miss any case of endometrial atypical hyperplasia or cancer.

Impact statement:

What is already known about this topic:

Unlike women with PMB in whom endometrial thickness (ET) ≤4mm is considered as low risk for endometrial hyperplasia and cancer, in postmenopausal women without PMB, the threshold that separates normal from pathologically thickened endometrium has not been standardized. A decision-analysis study in a hypothetical cohort found that ET threshold of 11mm yields a similar separation as ≤4mm in those with PMB.

What does this paper add?

The study uses prospectively collected data from consecutive patients using standardized format, thus minimizing bias from incomplete data. This study is the third prospective series in the literature to address the dilemma of management of asymptomatic postmenopausal women with incidental finding of thickened endometrium. It showed that the prevalence of endometrial atypical hyperplasia and cancer is high enough to justify investigation and for the clinical problem not to be trivialized. All cases of endometrial atypical hyperplasia and cancer had endometrial thickness of ≥10mm.

Clinical implications and future research:

Our data strengthen the current body of literature to help development of clinical practice guidelines about the management work-up. However, a well-designed multi-centre large prospective study is required to confirm the findings since most studies in the literature are either retrospective or small.

Keywords

Endometrial cancer; endometrial hyperplasia; endometrial polyp; endometrial thickness; postmenopausal bleeding

Introduction

Trans-vaginal ultrasound scan (TVS) is frequently performed in postmenopausal women referred for a variety of symptoms, such as pelvic pain or bloating. Although concerns regarding endometrial pathology may not have been the indication for the test, endometrial thickness (ET) is often measured. The incidental finding of ET> 4mm in the absence of postmenopausal bleeding (PMB) is a common cause of referral to secondary care, and can lead to a cascade of interventions to exclude endometrial hyperplasia or cancer (Jade et al., 2016). There is lack of consensus amongst gynecologists about its significance, and there are no evidence-based guidelines to inform clinical practice as how these women are best managed, leading to wide variations in practice (Gambacciani et al., 2004, Giannella et al., 2014).

Ninety percent of women with endometrial cancer present with PMB, and women with PMB have a 5-10% chance of having endometrial cancer (Bachmann et al., 2003, ACOG, 2009). However; it is estimated that up to 15% of endometrial cancers occur in women without PMB (NIH National Cancer Institute, 2000). It is well established that ET ≤4mm in women with PMB is associated <1% risk of endometrial cancer; therefore, these women are usually reassured without the need for further investigations (ACOG, 2009, RCOG, 2016). However; in postmenopausal women without PMB, the threshold that separates normal from pathologically thickened endometrium has not been standardized. Smith-Bindman *et al* performed a decision analysis study, in a theoretical cohort of 10 000 postmenopausal women aged ≥ 50 years using published and unpublished data, to determine the ET threshold that should be considered abnormal in asymptomatic postmenopausal women. They found that in a postmenopausal woman with PMB, the risk of endometrial cancer is approximately 0.07% if the endometrium is

thin (≤5 mm) and 7.3% if her endometrium is thick (>5mm). In a postmenopausal woman without PMB, an 11mm threshold yields a similar separation between women who are at high risk and low risk for endometrial cancer. The risk of cancer is approximately 0.002% if the endometrium is thin (≤11 mm) and 6.7% if the endometrium is thick (>11 mm). If an ET threshold of 4 mm was used to define an abnormal test result, as in women with PMB, the number of false-positive test results would far outnumber the true-positive test results (Smith-Bindman et al., 2004).

In addition, two previous studies found that endometrial polyps are the commonest pathology encountered in postmenopausal women with asymptomatic increase in ET. The reported prevalence varied between 34%-73%, and hysteroscopy was recommended as the first line investigation tool (Farfaras et al., 2011, Schmidt et al., 2009).

Given the current controversy surrounding the significance and management of thickened endometrium of >4mm in postmenopausal women without PMB, this study was conducted to (1) quantify the prevalence of endometrial hyperplasia, cancer and polyps, (2) determine the optimum ET threshold that should be considered abnormal and trigger further investigations. The aim was to produce data to help the development of clinical practice guidelines about the management work-up.

Materials and methods

The routine demographic and clinical data of the PMB clinic was collected prospectively in a password-protected Microsoft Access database, and then was extracted anonymously and compiled on a Microsoft Excel spreadsheet (Microsoft corporation 2010, Redmond, WA, USA). The database contained the details of 1995 consecutive women referred to Sandwell and West Birmingham Hospitals NHS Trust, West Midlands, UK between 1st January 2011 and 31st January 2015. The study group included 81 (4.1%) postmenopausal women with incidental finding of ET >4mm in the absence of PMB.

The TVS and histopathology reports were accessed using the electronic Clinical Data Archive (CDA, 2007) System that was developed by the IT department of the Trust as a repository of patients' administrative and clinical data. The case notes were reviewed for women undergoing hysteroscopic (diagnostic or therapeutic) procedure to obtain the operation findings.

All postmenopausal women with incidental finding of ET >4mm without PMB were offered Pipelle endometrial biopsy. However, the decision to perform hysteroscopy was individualized after the discussion between the patient and consultant. Women were categorized according to the investigation results into: (i) Group 1: benign endometrium (including benign endometrial polyps), and (ii) Group 2: endometrial atypical hyperplasia and cancer. Endometrial atypical hyperplasia and cancer were combined as a single disease. This is because of the high rate of undercall and progression to cancer when atypical hyperplasia is found (Smith et al., 2014, Gallos et al., 2013).

Statistical analysis

Statistical analyses were carried out using IBM® SPSS® Statistics for windows software version 20 (International Business Machines (IBM) corporation, Armonk, NYC, USA). Continuous variable indices are presented as mean with standard deviation or as median with inter-quartile range (IQR) as distribution demands.

Receiver operator characteristic (ROC) curve was used to identify the ET cut-off point for pathological endometrium. From the ROC curve, we calculated the area under the curve (AUC) with 95% confidence interval (95%CI), p value, sensitivity and specificity for the relevant cut-off point. The following equation was used to define the optimum cut-off point (Indrayan, 2013):

$$\sqrt{(1-sensitivity)^2+(1-specificity)^2}$$

Fisher's Exact test was used to find the statistical association between the ET cut-off point and the outcome.

Data were collected as part of the routine investigations and treatment, and the project was considered as "service evaluation"; therefore, ethics approval was not deemed necessary. Service evaluation may not require ethical approval in the UK (NHS Health Research Authority, 2011, UCL Research Ethics Committe 2015).

Results

The prevalence of endometrial atypical hyperplasia and cancer was 4/81 (4.9%) and benign endometrial polyps was 20/81 (24.7%) in postmenopausal women with incidental finding of ET >4mm without PMB. Women's characteristics and investigations findings are shown in table 1 and table 2, respectively. Three women were diagnosed with endometrial cancer. The first was 86-year-old, body mass index (BMI) was not measured as she was wheel-chair dependent, and the ET was 25mm. The second was 75-year-old, BMI was 26, and the ET was 12mm. The third was 83-year-old, BMI was 26, and the ET was 10mm. One woman was diagnosed with endometrial atypical hyperplasia who was 57-year-old, BMI was 33, and the ET was 16mm. None of these four women was a user of HRT or Tamoxifen.

The ROC curve (Figure 1) identified the ET threshold for diagnosing endometrial atypical hyperplasia and cancer as ≥10mm with sensitivity of 100% (95% CI=40-100%), specificity of 60% (95% CI=48-71%), AUC=0.8 (95% CI=0.66-0.93), $p<0.04$.

The outcome of investigations using ≥10mm endometrial thickness threshold is summarized in table 3. The prevalence of endometrial atypical hyperplasia and cancer was significantly high with ET ≥10mm, $p=0.03$. For the 35 women with ET ≥10mm, the prevalence of endometrial atypical hyperplasia and cancer was 4/35 (11.4%) and benign endometrial polyps was 16/35 (45.7%).

Discussion

To our knowledge, this is the third prospective study to address the dilemma of management of postmenopausal women referred to secondary care with thickened endometrium without PMB. The prevalence of endometrial atypical hyperplasia and cancer was 4.9% and benign endometrial polyps was 24.7%. The ROC curve identified the ET cut-off level for endometrial atypical hyperplasia and cancer to be ≥10mm.

In their prospective series, Schmidt *et al* reported similar prevalence of endometrial atypical hyperplasia and cancer (4.9%), but higher prevalence of endometrial polyps (73.3%) (Schmidt et al., 2009), while Giannella *et al* found the prevalence to be 2.1% and 34%, respectively (Giannella et al., 2014). The other three published series in the past decade were retrospective carrying the risk of bias from heterogeneity and missing data. They reported wide variations in the prevalence of endometrial atypical hyperplasia and cancer (1.3%-13.2%) and endometrial polyps (27.2%-59.1%) (Famuyide et al., 2014, Saatli et al., 2014, Yasa et al., 2016). In particular, the high prevalence of endometrial atypical hyperplasia and cancer (70/530, 13.2%) in Saatli *et al* study is hard to explain since it is much higher than the reported prevalence of the disease in women with PMB which varied in the literature between 5-10% (ACOG, 2009, Bachmann et al., 2003).

Ninety percent of women with endometrial cancer present with PMB as previously mentioned. (Bachmann et al., 2003, ACOG, 2009). Nonetheless, there is likely a preclinical phase during which some cancers might be detectable prior to the development of symptoms. In addition,

some cancers do not present with bleeding until they progressed beyond Stage I (Smith et al., 2014). The National Institute for Health and Care Excellence (NICE) sets a 3% positive predictive value to trigger referrals to secondary care for investigations for suspected cancer (NICE, 2015). In this study, the endometrial atypical hyperplasia and cancer prevalence of 11.4% indicates that referral of postmenopausal women with incidental finding of thickened endometrium ≥10mm is warranted.

Giannella *et al* tested the diagnostic accuracy of various ET cut-off values by comparing histological and hysteroscopic findings in asymptomatic postmenopausal women with ET>4mm. They found that no ET cut-off values had optimal diagnostic accuracy, but an ET cut-off value >10 mm did not miss any cases of endometrial atypical hyperplasia or cancer. At this cut-off value, the atypical hyperplasia and cancer rate was 9.4%. On using ET cut-off value >4 mm, 97% of performed hysteroscopies revealed a benign intra-uterine pathology (Giannella et al., 2014). Smith-Bindman *et al* concluded after the decision-analysis study that no cut-off is perfect, and cancer will be missed no matter what cut-off is used. However, using a threshold of 11 mm seems to provide an acceptable trade-off between cancer detection and unnecessary biopsies prompted by an incidental finding (Smith-Bindman et al., 2004). In this study, the ≥10mm threshold identified by the ROC curve had sensitivity of 100%, which would be more reassuring to clinicians than 11mm cut-off.

Our data strengthens the current body of literature to help development of clinical practice guidelines about the management work-up. The data were collected prospectively, consecutively,

and in a standardized fashion, minimizing bias from incomplete data. We included a homogeneous cohort of postmenopausal women referred to secondary care with incidental finding of ET >4mm without PMB. Nonetheless, given the small sample size, we could not include in the analysis women's characteristics and risk factors for endometrial hyperplasia and cancer such as age and body mass index.

A well-designed multi-center large prospective study is required to reach consensus about the optimum ET cut-off to initiate investigation in asymptomatic postmenopausal women with incidental finding of thickened endometrium. This study showed that the prevalence of pathology is high enough to justify investigation and for the clinical problem not to be trivialized by women and doctors alike. The use of ≥10mm ET threshold to prompt investigations may be acceptable since it is unlikely to miss endometrial atypical hyperplasia or cancer.

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Conflict of interest

The authors declare no conflicts to interest.

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Tables and figures legends

Table 1: Characteristics of postmenopausal women referred with incidental finding of ET >4mm without PMB (*n*=81)

Table 2: Investigations findings of postmenopausal women referred with incidental finding of ET >4mm without PMB (*n*=81)

Table 3: The outcome of investigations using ≥10mm endometrial thickness threshold

Figure 1: Endometrial thickness receiver operator characteristic (ROC) curve for endometrial atypical hyperplasia and cancer. Arrow indicates the point where the 10mm endometrial thickness lies on the curve; Area under the curve (AUC) for the endometrial thickness cut-off ≥10mm is 0.8, 95% confidence interval (CI)=0.66-0.93, *p*=0.04, sensitivity = 100% (95% CI=40-100%), specificity = 60% (95% CI=48-71%)

Table 1: Characteristics of postmenopausal women referred with incidental finding of ET >4mm without PMB (*n*=81)

Variable	
Age in years, mean (±SD)	68.2 (9.8)
LMP in years, mean (±SD)	15 (6.4)
BMI, median (IQR)	29 (8)
HRT users	
Yes, *n* (%)	5 (6.2%)
No, *n* (%)	76 (93.8%)
Tamoxifen users	
Yes, *n* (%)	6 (7.4%)
No, *n* (%)	75 (92.6%)

BMI=Body mass index ET=Endometrial thickness

HRT=Hormonal replacement therapy LMP=Last menstrual period

IQR=Interquartile range SD=Standard deviation

Table 2: Investigations findings of postmenopausal women referred with incidental finding of ET >4mm without PMB (*n*=81)

Variable	
ET in mm, mean (±SD)	10.3 (6.3)
Benign endometrium, *n* (%)	77 (95.1%)
Endometrium with no hyperplasia or cancer, *n* (%)	57 (70.4%)
Benign endometrial polyp, *n* (%, 95%CI)	20 (24.7%, 16-35.7%)
Atypical endometrial hyperplasia and cancer, *n* (%, 95%CI)	4 (4.9%, 1.6-13%)

ET=endometrial thickness

CI=confidence interval

SD=standard deviation

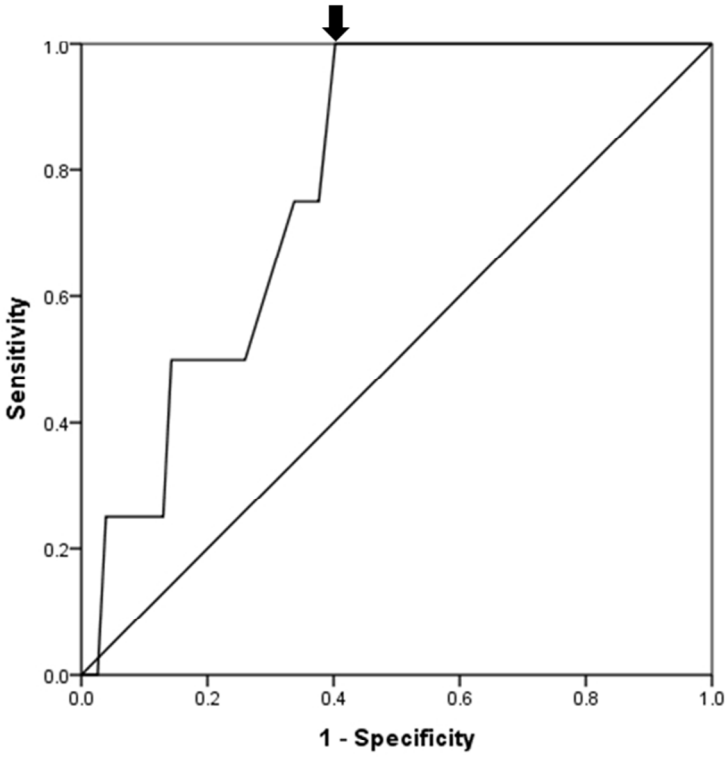
Table 3: The outcome of investigations using ≥10mm endometrial thickness threshold

Variable	**ET ≥10mm** ***n* (%)**	**ET <10mm** ***n* (%)**	***p* value**
Benign endometrium			
Endometrium with no hyperplasia or cancer	15 (42.9%)	42 (91.3%)	
Benign endometrial polyp	16 (45.7%)	4 (8.7%)	
Endometrial atypical hyperplasia and cancer	4 (11.4%)	0	0.03*
Total	35	46	

ET=endometrial thickness

CI=confidence interval

**p* is measured by Fisher's Exact test and considered significant when <0.05



Endometrial thickness receiver operator characteristic (ROC) curve for endometrial atypical hyperplasia and cancer. Arrow indicates the point where the 10mm endometrial thickness lies on the curve; Area under the curve (AUC) for the endometrial thickness cut-off ≥10mm is 0.8, 95% confidence interval (CI)=0.66-0.93, p=0.04, sensitivity = 100% (95% CI=40-100%), specificity = 60% (95% CI=48-71%)

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